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disease

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Objective: To study whether lower arterial oxygen saturation (SaO₂) and chronic obstructive pulmonary disease (COPD) are associated with cerebral white matter lesions and lacunar infarcts.

Methods: We measured SaO₂ twice with a pulse oximeter, assessed the presence of COPD, and performed MRI in 1077 non-demented people from a general population (aged 60–90 years). We rated periventricular white matter lesions (on a scale of 0–9) and approximated a total subcortical white matter lesion volume (range 0–29.5 ml). All analyses were adjusted for age and sex and additionally for hypertension, diabetes, body mass index, pack years smoked, cholesterol, haemoglobin, myocardial infarction, and left ventricular hypertrophy.

Results: Lower SaO₂ was independent of potential confounders associated with more severe periventricular white matter lesions (score increased by 0.12 per 1% decrease in SaO₂ (95% confidence interval 0.01 to 0.23)). Participants with COPD had more severe periventricular white matter lesions than those without (adjusted mean difference in score 0.70 (95% confidence interval 0.23 to 1.16)). Lower SaO₂ and COPD were not associated with subcortical white matter lesions or lacunar infarcts.

Conclusion: Lower SaO₂ and COPD are associated with more severe periventricular white matter lesions.

Cerebral white matter lesions and lacunar brain infarcts are frequently observed on magnetic resonance imaging scans of elderly people.^{1–4} Evidence is accumulating that these lesions play an important role in the development of cognitive decline and dementia.^{5–7} Although the exact pathogenesis of these lesion is not fully understood, they are considered to be caused by ischaemic small vessel disease, with hypertension and increased age as the most important risk factors. Degenerative changes of cerebral small vessels result in narrowing and obstruction of the arteriolar lumen and alteration of the cerebral autoregulation, both resulting in hypoperfusion of the cerebral white matter and basal ganglia.⁸

In addition to cerebral perfusion, the arterial oxygen content determines the total amount of oxygen available in the brain. Low arterial oxygen pressure strongly aggravates brain damage caused by cerebral hypoperfusion. Pure hypoxaemic insults, however, fail to cause brain damage.⁹ Whether lower arterial oxygen pressure in elderly people plays a role in the pathophysiology of white matter lesions is unknown.

The assessment of the arterial oxygen pressure is a relatively invasive procedure and therefore not applicable in a large population based study. The oxygen saturation of haemoglobin, as assessed by pulse oximetry, is a non-invasive measurement that gives an indication of the arterial oxygen pressure. We studied the association between arterial oxygen saturation (SaO₂) and white matter lesions and lacunar infarcts. Chronic obstructive pulmonary disease (COPD) is a common disease among elderly people.^{10–13} Patients with COPD experience oxygen deprivation for prolonged periods, especially during physical exercise, exacerbation of disease, and sleep.^{14–15} We therefore also examined the association between COPD and white matter lesions and lacunar infarcts.

in the elderly. Over the period 1995–96, we randomly selected participants aged 60–90 years by sex and 5 year age strata from the population based Zoetermeer¹⁶ and Rotterdam¹⁷ studies. These populations were almost entirely white. A total of 1077 non-demented elderly persons participated in our study (overall response 63%).³ Each person gave informed consent to participate in our study, which had been approved by the local medical ethics committee.

Arterial oxygen saturation and COPD

All participants underwent an interview and a physical examination at the time of MRI scanning. SaO₂ was measured twice, 5 minutes apart, with a pulse oximeter (Oxycount; Andos, Hamburg, Germany) on the right index finger. The two measurements were averaged (correlation coefficient was 0.73 and the range was 88–99%).

Participants were asked to bring all their prescription drugs with them to the research centre. The research physicians recorded these and checked their indication. COPD was considered present if a person was taking inhalation medication from at least one of the following groups: sympathomimetics, parasympatholytics, or glucocorticosteroids.

Measurements of other covariates

Blood pressure was measured twice on the right arm with a random zero sphygmomanometer, and the average of these two measurements was used. Hypertension was defined as a systolic blood pressure of ≥ 140 mm Hg, a diastolic blood pressure of ≥ 90 mm Hg, and/or the use of blood pressure lowering medication.

We collected non-fasting blood samples from all participants. We considered diabetes mellitus to be present if a person used oral anti-diabetics or insulin and/or had a

METHODS

Study sample

The Rotterdam Scan Study was designed to study the aetiology and natural history of age related brain changes

Abbreviations: COPD, chronic obstructive pulmonary disease; SaO₂, arterial oxygen saturation

glucose level ≥ 11.1 mmol/l. The body mass index was calculated as weight (kg) divided by height squared (m^2). A research physician obtained information on smoking habits using a structured questionnaire. Patients were categorised as having smoked or never smoked. Furthermore, we calculated for every participant the number of pack years smoked (number of cigarettes per day \times years of smoking/20). Serum total cholesterol levels were measured from non-fasting blood samples using an automated enzymatic method. The presence of left ventricular hypertrophy and myocardial infarction was assessed by MEANS interpretation of a 12 lead electrocardiogram (Acta electrocardiograph; Esaote, Florence, Italy).¹⁸ Haemoglobin levels were assessed using a standard and validated method.¹⁹

Cerebral white matter lesions and lacunar infarcts

All participants underwent MRI scanning of the brain. We made axial T1, T2, and proton density weighted scans on 1.5 T MRI scanners (MR Gyroscan; Philips, Best, the Netherlands, and MR Vision; Siemens, Erlangen, Germany). The slice thickness was 5 or 6 mm (scanner dependent) with an inter-slice distance of 1 mm.

White matter lesions were considered present if visible as hyperintense signals on proton density and T2 weighted images, without prominent hypointensity on T1 weighted scans. When the largest diameter of the white matter lesion was directly adjacent to the ventricle, it was defined as periventricular, otherwise as subcortical. The scoring method has been described in detail previously.²⁰ Briefly, periventricular white matter lesions were rated semiquantitatively from 0 (no lesion) to 3 (large confluent lesion) at three regions (adjacent to the frontal horns, the lateral walls, and the occipital horns of the lateral ventricle). We added the sum of the region specific scores to acquire a total periventricular white matter lesion score (range 0–9). We counted subcortical white matter lesions in three size categories based on their maximum diameter: small (<3 mm), medium (3–10 mm), and large (>10 mm). A total volume was approximated by assuming these subcortical lesions to be spherical with a fixed maximum diameter (volume range 0–29.5 ml). Both inter- and intra-reader studies ($n = 100$) showed good to excellent agreement (for periventricular white matter lesion grade the kappa values were 0.79 and 0.90, respectively, and for subcortical white matter lesion volume the intra-class correlation coefficients were 0.88 and 0.95, respectively). We defined lacunar infarcts as focal hyperintensities on T2 weighted images 3–20 mm in size and located in the subcortical white matter or basal ganglia. Proton density scans were used to distinguish infarcts from dilated perivascular spaces. Lesions in the white matter also had to have corresponding prominent hypointensities on T1 weighted images for us to distinguish them from cerebral white matter lesions.

Data analysis

The relation of SaO_2 and periventricular and subcortical white matter lesions was analysed using multiple linear regression models with SaO_2 categorised in tertiles and subsequently with SaO_2 as a continuous variable. We used linear regression analysis to calculate adjusted mean differences of periventricular white matter lesion score and subcortical white matter lesion volume between participants with and without COPD. We analysed the association between SaO_2 and COPD and the presence of lacunar infarcts by multiple logistic regression analysis; from these analyses all people with cortical infarcts were excluded ($n = 33$). All analyses were adjusted for age and sex and additionally for hypertension, diabetes, body mass index, pack years smoked, cholesterol level, haemoglobin concentration, myocardial

infarction, and left ventricular hypertrophy. We performed supplementary analysis separately for those patients who had ever smoked and those who had never smoked. All regression analyses were followed by residual analysis to confirm assumptions of the model.

RESULTS

Table 1 gives selected characteristics of the study population. We measured SaO_2 for all participants, except for 11 subjects for whom we could not get a signal from the oximeter. These 11 people did not differ in the presented characteristics from the participants that had complete data. Seventy three participants had COPD; 31 (43%) had chronic bronchitis, 9 (12%) had lung emphysema, and 33 (45%) had a combination of both or was not further specified.

SaO_2 was on average lower in men, those who were ever cigarette smokers, and higher age. Participants with COPD were on average older, more often men, and were more often ever cigarette smokers. The unadjusted mean SaO_2 was 0.84% (95% confidence interval (CI) 0.55 to 1.13%) lower in participants with COPD than in those without. Among the smokers, those with COPD smoked on average more pack years than those without COPD.

Fig 1 shows the association between SaO_2 in tertiles (means 95.3%, 96.7%, and 97.8%) and white matter lesions. People in the lowest tertile of SaO_2 had more severe periventricular white matter lesions than those in the upper tertile, but did not have more severe subcortical white matter lesions. The age and sex adjusted mean periventricular white matter lesion score increased by 0.12 per 1% decrease in SaO_2 (95% CI 0.02 to 0.21). After additional adjustment for hypertension, diabetes mellitus, body mass index, smoked pack years, cholesterol level, haemoglobin concentration, myocardial infarction, and left ventricular hypertrophy, this association remained unaltered (periventricular white matter lesions score increased by 0.12 per 1% decrease in SaO_2 (95% CI 0.01 to 0.23)). Arterial oxygen saturation was not associated with volume of subcortical white matter lesions (0.06 ml increase per 1% decrease in SaO_2 (95% CI -0.07 to 0.20)) or the risk of lacunar infarcts (odds ratio 1.01 per 1% decrease in SaO_2 (95% CI 0.89 to 1.15)), adjusted for age and sex. The association between SaO_2 and periventricular white matter lesion severity was not different for those who had ever and those who had never smoked (increment of 0.12 (95% CI -0.02 to 0.25) v 0.11 (95% CI -0.08 to 0.30) per 1% decrease in SaO_2 in the fully adjusted model).

Table 1 Characteristics of the study population in 1995–1996

	All participants (n = 1077)
Age, years	72.2 (7.4)
Women, %	51.5
Hypertension, %	73.0
Diabetes mellitus, %	7.0
Body mass index, kg/m^2	26.7 (3.6)
Ever smoked cigarettes, %	66.4
Smoking, pack years	19.1 (24.0)
Total cholesterol, mmol/l	5.9 (1.0)
Haemoglobin, mmol/l	8.7 (0.7)
Left ventricular hypertrophy, %	2.9
Myocardial infarction, %	10.3
Oxygen saturation, % SaO_2	96.5 (88–99)
Lacunar infarcts, %*	21.6
White matter lesion severity	
Periventricular, score 0–9	2.4 (2.2)
Subcortical, ml	1.4 (2.9)

Values are percentages or unadjusted means (SD), or for oxygen saturation the median (range).

*People with cortical infarcts were excluded ($n = 33$).

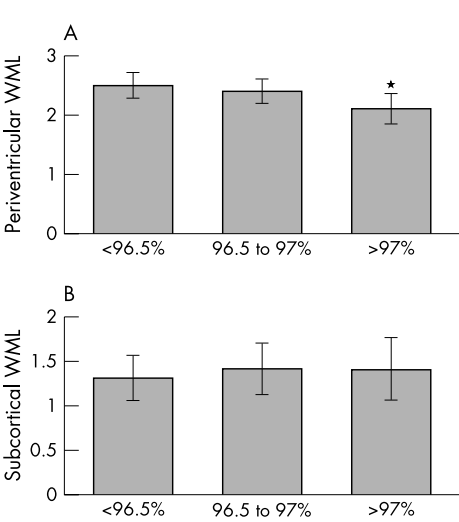


Figure 1 Association between tertiles of arterial oxygen saturation and severity of periventricular (A) and subcortical (B) white matter lesions (mean score or volume adjusted for age, sex, hypertension, diabetes mellitus, body mass index, pack years smoked, cholesterol level, haemoglobin concentration, prevalent myocardial infarction, and left ventricular hypertrophy with 95% confidence intervals). *Significance: $p=0.01$ for difference between first and third tertile

Participants with COPD had more severe periventricular white matter lesions than those without (table 2). This difference was independent of vascular risk factors, and observed in both ever and never cigarette smokers (age and sex adjusted difference for those who had ever (0.59 (95% CI 0.08 to 1.11) and never (1.11 (95% CI 0.08 to 2.14) smoked). Participants with and without COPD did not differ in subcortical white matter lesion volume (table 2) or the risk of lacunar infarcts (age and sex adjusted odds ratio 1.00 (95% CI 0.54 to 1.87)).

DISCUSSION

In this population based study, we found that lower SaO₂ was associated with more severe periventricular white matter lesions, but not with subcortical white matter lesions or lacunar infarcts. This association was independent of vascular risk factors, haemoglobin concentration, and measurements of cardiac function. Furthermore, we found that participants with COPD had more severe periventricular white matter lesions, but did not differ in subcortical white matter lesion volume or in prevalence of lacunar infarcts.

The strengths of this study are the population based design and the large number of elderly participants for whom MRI scans were performed. Before interpreting the results, we must address some methodological issues. The pulse oximeter accurately and precisely measures SaO₂ within the range 70 to 100% compared with measures assessed by blood gas analysis.^{21 22} All SaO₂ measurements presented in this paper were in this range. In 11 participants, the pulse oximeter failed to give a signal, probably caused by cold fingers or low peripheral perfusion. We do not think that the exclusion of this small group, which did not differ from the study population with respect to the measured covariates or outcome variables (data not shown), has markedly influenced our results.

SaO₂ is an indirect measure of arterial oxygen pressure in the cerebral arteries. The SaO₂ is linked to the arterial oxygen pressure by the oxygen–haemoglobin dissociation curve. Changes in blood CO₂ concentration, temperature, and 2,3-diphosphoglycerate concentration shift the dissociation curve.²³ We did not measure these variables, but we

Table 2 Mean differences (95% confidence interval) of periventricular white matter lesion score and subcortical white matter lesion volume (ml) between participants with and without COPD

Excess white matter lesions in participants with COPD				
Model	Periventricular score (95% CI)	p	Subcortical volume (95% CI)	p
1*	0.70 (0.23 to 1.16)	<0.01	0.43 (−0.21 to 1.08)	0.19
2†	0.69 (0.23 to 1.14)	<0.01	0.43 (−0.22 to 1.08)	0.20

*Adjusted for age and sex.
†Adjusted for age, sex, hypertension, diabetes mellitus, body mass index, cholesterol level, pack years smoked.
CI, confidence interval.

performed the oximetry for each patient under comparable circumstances. Furthermore, pulse oximetry assesses SaO₂ in arterial blood, whereas these factors mainly affect the relation between oxygen saturation and oxygen pressure in capillary blood.²³ We therefore think that SaO₂ gives a good indication of the arterial oxygen pressure.

Defining COPD as the use of medication for this indication may have introduced misclassification. COPD cases that were not being treated will have been missed, and this may explain why the prevalence of COPD in our study is somewhat lower than in some other population based studies.^{10 11 13} However, the age and sex specific prevalence of COPD in our study was comparable with a large Canadian study using health questionnaires.¹² Both SaO₂ and the presence of COPD were assessed without knowledge of other risk factors or presence of white matter lesions. The MRI scans were rated by researchers blinded to all other data. Therefore, any misclassification in the assessment of SaO₂ or COPD will be random and result in an underestimation of the strength of any association.

People with lower SaO₂ had significantly more severe periventricular white matter lesions. However, the differences were not very large and probably do not represent clinically significant disturbances on an individual level. It should be noted that we studied a large cohort of non-demented elderly people representative of the general population and not a selected group of patients. Consequently, the majority of the participants had SaO₂ values within the normal range. Within this population based range we found that a decrease in SaO₂ was associated with an increase in periventricular white matter lesion severity. This observation was supported by the consistent result with COPD.

In the Cardiovascular Health Study, an association between lower forced expiratory volume in 1 second (a measure of lung function) and white matter lesion severity was observed.¹ In that study, the association disappeared after adjusting for sex and history of smoking. Smoking is the most important determinant of COPD.^{11 13} However, we also observed an association between COPD and white matter lesions in subjects who had never smoked, indicating that this relation was not based on the potential confounding effect of smoking.

Chronic hypoperfusion is thought to play an important role in the development of white matter lesions. Experimental studies show that hypoxaemia in the absence of a reduced cerebral blood flow does not result in neuronal damage.^{24–26} Hypoxaemia additional to hypoperfusion, however, strongly exacerbates ischaemic brain damage.⁹ This difference in effect between pure hypoxaemia and the combination of hypoxaemia and ischaemia may be explained by the physiological increase in cerebral blood flow under conditions of reduced blood oxygen content.²⁷ In our study, we did not assess the cerebral blood flow of the cerebral white matter.

Therefore we can only speculate on the interaction between ischaemia and hypoxaemia in the development of white matter lesions.

The periventricular white matter is an arterial border zone and therefore relatively hypoperfused, in particular when total cerebral blood flow decreases and autoregulation is impaired.²⁸ Areas with severe white matter lesions show hypoperfusion on perfusion weighted MRI and PET scan studies.^{29–31} Furthermore, vasomotor reactivity is diminished in people with severe white matter lesions.^{32–33} As a consequence, the physiological compensation of hypoxaemia might be insufficient in people with cerebral small vessel disease, especially in border zone areas. Altered cerebral autoregulation may be the main cause of periventricular white matter lesions, whereas concentric narrowing of the arteriolar lumen may be the main cause of subcortical white matter lesions and lacunar infarcts. Lower SaO₂ is possibly more detrimental in combination with chronic or intermittent hypoperfusion, as in disturbed autoregulation, than in instances of acute hypoperfusion, as in arteriolar obstruction.²⁵

In conclusion, our study shows that COPD and lower SaO₂ are associated with more severe periventricular white matter lesions. This finding suggests that not only cerebral hypoperfusion, but also hypoxaemia may contribute to the aetiology of periventricular white matter lesions.

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Arterial oxygen saturation, COPD, and cerebral small vessel disease

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